The Scope of The Problem

US Prevalence: 1.8% are chronically infected with Hepatitis C virus (HCV)

Hepatitis C is Underdiagnosed in US

HIV=human immunodeficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus

Chronic Hepatitis C Infection in US
(many populations not accounted for in surveillance studies)

- ≥5.2 million living with chronic HCV in US
  - Prevalence: 1.8%
- Chronic HCV cases not included in NHANES estimate
  - Homeless (n=142,761-337,610)
  - Incarcerated (n=372,756-664,826)
  - Veterans (n=1,237,461-2,452,006)
  - Active military (n=438k)
  - Healthcare workers (n=64,809-259,234)
  - Nursing home residents (n=63,609)
  - Chronic hemodialysis (n=20,578)
  - Hemophiliacs (n=12,971-17,000)

Estimated Hepatitis C Cases

Conservative estimate
Upper limit of estimate

Incarcerated (n=372,754-664,826)

Veterans (n=1,237,461-2,452,006)

Healthcare workers (n=64,809-259,234)

Nursing home residents (n=63,609)

Chronic hemodialysis (n=20,578)

Hemophiliacs (n=12,971-17,000)

Hepatitis C-Related Cirrhosis Is Projected to Peak Over Next 10 Years

25% of patients with HCV currently have cirrhosis

37% of patients with HCV are projected to develop cirrhosis by 2020, peaking at 1 million

Annual Age-adjusted Mortality Rates from HBV, HCV, and HIV

CDC HCV Testing Recommendations

1998:
- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organ before July 1992
- Ever on chronic hemodialysis
- Evidence of liver disease (elevated ALT)
- Infants born to HCV-infected mothers
- HIV infection

2012:
- Adults born 1945-1965 receive 1-time HCV testing
- All persons with HCV infection: brief alcohol screening/intervention as appropriate, referral to treatment services


HCV Infection Testing Algorithm

- Anti-HCV Point-of-care Immunoreagent (Rapid Test) or Bench immunoassay (EIA, CIA, MEIA, CMIA)
- Reactive (+) or Negative (-)
- Positive (†): Active / Current HCV infection
- Refer to Care and Treatment
- Negative (-)
- If immunocompromised status or acute infection is suspected, test for HCV RNA
- If ongoing risk factors eg, injecting drug use or other recent exposures, repeat anti-HCV testing > 6 months after most recent exposure

Genotype and Viral Load in US Patients

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Viral Load</th>
<th>49.5%</th>
<th>24.5%</th>
<th>14.7%</th>
<th>4.7%</th>
<th>3%</th>
<th>2.7%</th>
<th>1.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>HVL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>High</td>
<td>49.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>Low</td>
<td>24.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 4,5,6</td>
<td>High</td>
<td>14.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 4,5,6</td>
<td>Low</td>
<td>4.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Why Do We Treat Chronic HCV?

Majority of those infected develop chronic disease.

ALT (U/L)

- 0
- 200
- 400
- 600
- 800
- 1000

Years After Exposure

- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 40
- 45
- 50

Fibrosis → Cirrhosis

HCC

HCV RNA

Anti-HCV

Why Do We Treat Chronic HCV?

Majority of those infected develop chronic disease.

ALT (U/L)

- 0
- 200
- 400
- 600
- 800
- 1000

Years After Exposure

- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 40
- 45
- 50

Fibrosis → Cirrhosis

HCC

HCV RNA

Anti-HCV

Sustained virological response (SVR):

- Undetectable HCV RNA measured by PCR 24 weeks after therapy.
- Durable: HCV negative 99.2% of 1343 patients after 4.1 years.¹
- 100% in 433 patients after 18 years.²
- Slows and even reverses hepatic fibrosis.
- Improved morbidity and mortality with SVR.
- SVR with cirrhosis: less ascites, encephalopathy, variceal bleeding, hepatocellular carcinoma, and transplantation.

SVR = CURE


Two (2) Protease Inhibitors Approved for Genotype 1 (G1) HCV Infection

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Additional Regimen Components</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir 800 mg TID (q7-9hrs)²</td>
<td>PegIFN alfa + weight-based RBV</td>
<td>Naive to previous therapy, previous treatment failure, compensated cirrhosis, RGT.</td>
</tr>
<tr>
<td>Telaprevir 750 mg TID (q7-8hrs)³</td>
<td>PegIFN alfa + weight-based RBV</td>
<td>Naive to previous therapy, previous treatment failure, compensated cirrhosis, RGT.</td>
</tr>
</tbody>
</table>

For patients with genotype 2/3 infection, HCV therapy with PegIFNRBV (PR) remains the standard of care.

RGT: response-guided therapy

Data to Assemble Prior to Referring for Treatment

- HCV genotype 1a/1b
- Quantitative viral level
- IL-28B genotype
- Previous viral kinetics if non-responder
  - IL-28B not as helpful with accurate viral kinetics
- Fibrosis assessment
  - Liver imaging
- Concomitant medicines/Drug-drug interaction query
- Management plan for side effects
  - Rash, anemia, GI side effects
- Set expectations with patients
  - Time for approval, compliance

A Polymorphism on Chromosome 19 Predicts SVR: IL-28B

[Diagram showing the polymorphism on Chromosome 19.

IL-28B CC Genotype Associated With SVR

[Graph showing statistical analysis of SVR with IL-28B genotypes.

Fibrosis Assessment: Very Important in This Transition Era

- To treat or not to treat
  - Efficacy of new therapies largely determined by PR responsiveness
  - Achieving SVR in cirrhotic HCV patients is highly beneficial
  - Preliminary data with new oral therapies shows higher efficacy/shorter duration/less side effects
  - Limited data in cirrhosis patients
- Prognosis
  - Cirrhotic patients require regular screening for hepatocellular carcinoma, varices, other complications

Fibrosis Tests Available in 2013

- Liver biopsy: Gold standard
- Imaging of the liver:
  - Axial CT/MRI, US can demonstrate cirrhotic morphology, portal hypertension
- Serum Markers of Fibrosis: FIBROSpect®, FibroSURE®, APRI, FIB-4
- Elastography: Available at limited US centers
- AASLD Guideline
  - Liver biopsy should be considered if more information is desired for prognostic purposes or to make a decision regarding treatment
  - Currently available noninvasive tests may be useful in defining presence or absence of advanced fibrosis, but should not replace liver biopsy in routine clinical practice

Factors Predictive of Response to PR-based Therapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2/3</td>
<td>Lack of steatosis/insulin resistance</td>
<td>Race/ethnicity</td>
</tr>
<tr>
<td>No advanced fibrosis</td>
<td>Adherence</td>
<td>Low viral load</td>
</tr>
<tr>
<td>Low viral load</td>
<td>Rapid viral response (RVR)</td>
<td>Absence of cirrhosis</td>
</tr>
<tr>
<td>Younger age</td>
<td>Ribavirin dosage</td>
<td>Statin use</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>Race/ethnicity</td>
<td>IL-28B</td>
</tr>
<tr>
<td>Female</td>
<td>IL-28B</td>
<td>Genotype 1a/b</td>
</tr>
<tr>
<td>Weight</td>
<td>Anemia</td>
<td>On treatment viral response</td>
</tr>
</tbody>
</table>

Clinical Pharmacology and Drug Interactions

- Boceprevir (BOC)
  - Strong inhibitor of CYP3A4/5
  - Partly metabolized by CYP3A4/5
  - Potential inhibitor of and substrate for P-gp
- Telaprevir (TVR)
  - Substrate of CYP3A
  - Inhibitor of CYP3A
  - Substrate of P-gp
  - Must perform DDI survey or work with clinic pharmacology
- http://www.hep-druginteractions.org/

P-gp = p-glycoprotein


AASLD Guidelines for HCV Therapy

- Age ≥18, and
- HCV RNA positive, and
- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and
- Compensated liver disease (total serum bilirubin <15 g/dL; INR 1.5; serum albumin >3.4; platelet count 75 000 mm and no evidence of hepatic decompensation (hepatic encephalopathy and ascites), and
- Acceptable hematological and biochemical indices (HG 13 g/dL (men)/12 g/dL (women); neutrophil 1500/mm3 and serum creatinine <1.5 mg/dL), and
- Willing to be treated and adhere to treatment requirements.

“...It must be re-emphasized that the recommendations on the selection of patients for treatment are guidelines and not fixed rules; management and treatment considerations should be made on a case-by-case basis, taking into consideration the experience of the practitioner together with the acceptance of risk by the patient.”


TVR + PR in G1 Tx-Naïve Patients

Important Futility Milestones: Weeks 4, 12, 24

- Treatment duration: Patients with extended RVR (eRVR, undetectable* HCV-RNA at Week 4 and Week 12): receive 24 weeks of therapy
  - Patients without eRVR continue on PR for a total of 48 weeks

*Assay should have a lower limit of HCV RNA quantification ≤25 IU/mL for RGT

What Can We Tell Our Patients?
Significantly Higher SVR rates in TVR-Treated Patients
Compared to PR Alone

P < .0001

T12PR = telaprevir and pegylated interferon alfa-2a + ribavirin for 12 weeks, followed by peginterferon-ribavirin alone for
12 weeks if HCV RNA was undetectable at Week 12 or 36 weeks if HCV was detectable at either time point.
PR = placebo + PR for 12 weeks, then PR for 36 weeks.

ADVANCE Study: Influence of Race on SVR With PR ± TVR

PR+TVR PR

SVR / Cure Rate (%)

PR+TVR PR

Race White Black Race White Black

White 75 62 (19/26) 46 25 (7/28)
Black 75 62 (19/26) 46 25 (7/28)


Influence of Patient and Virus Factors on SVR With PR + TVR

SVR / Cure Rate (%)

Genotype 1b 1c HCV RNA Fibrosis

<800,000 ≥800,000 F0-F2 F3-F4

71 79 78 74 78 02

ADVANCE Study: Role of IL28B on SVR With PR±TVR

42% (454/1088) of patients available for IL28B analysis; all were White TVR associated with increased SVR rates across IL28B genotypes

TVR for All Non-responders

4-week PR lead-in neither improves nor reduces SVR rates

RGT therapy with relapers receiving 24 weeks of therapy who undergo eRVR
All others (nulls, partial responders, cirrhosis) 48 weeks

REALIZE: SVR in Prior Relapers, Prior Partial Responders, and Prior Null Responders

SVR (%)
REALIZE: SVR by Baseline Fibrosis Stage and Prior Response

Prior relapsers
Prior partial responders
Prior null responders

Pooled T12/PR48
Pbo/PR48


Lead-in Strategy: A Strategy to Determine Who to Treat

4 weeks of PR lead-in prior to BOC (or TVR):
- Lowers HCV RNA burden
- May identify rapid responders who may not need DAA
- Allows assessment of interferon responsiveness
  - Provides useful information regarding likelihood of SVR with addition of DAA
  - Clinicians can determine who can tolerate PR backbone
  - Assess hematologic response to PR therapy, especially in "marginal" patients; make needed dose adjustments before addition of DAA

SVR by Response at Week 4 in Lead-in Arm of REALIZE:
Is There a Role for Lead-in With PR Before TVR?

**BOC for G1 naive HCV**

**Milestones: Weeks 8, 12, 24**

- **Week 4**: PR lead-in
- **Week 28**: TW 8-24 HCV RNA Undetectable*
- **Week 12**: Follow-up
- **Week 24**: PR + BOC (44 weeks) for cirrhotic patients/poorly responsive pts
- **Week 48**: TW 1 HCV RNA Detectable/ Futility
- **Week 72**: Follow-up

*assay should have a lower limit of HCV-RNA quantification < 25 IU/mL, and limit of HCV RNA detection of approximately 10-15 IU/mL.


---

**SPRINT 2: SVR and Relapse Rates**

- **SVR**
- **Relapse Rate**

<table>
<thead>
<tr>
<th></th>
<th>Non-Black Patients</th>
<th>Black Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>48 P/R</strong></td>
<td>52%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>BOC</strong></td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>BOC/PR48</strong></td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>P</strong> = 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P</strong> = 0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


---

**SVR by Week 4 PR Lead-In Response**

A >1 log10 decrease in HCV RNA at week 4 of therapy is the strongest predictor of a SVR

<table>
<thead>
<tr>
<th></th>
<th>Non-Black Patients</th>
<th>Black Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>48 P/R</strong></td>
<td>60%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>BOC</strong></td>
<td>52%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>BOC/PR48</strong></td>
<td>52%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>P</strong> &gt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P</strong> = 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SPRINT-2 SVR: Influence of Patient and Virus Factors on SVR With PR + BOC


SPRINT-2: SVR by IL28B Polymorphism

62% of individuals (653/1048) had consented to IL-28B pharmacogenomic studies


BOC for G1 Non-responders HCV Key Time Points: Weeks 8, 12, 24

*assay should have a lower limit of HCV-RNA quantification <25 IU/mL, and limit of HCV RNA detection of approximately 10-15 IU/mL.

SVR by Historical Response Partial-responders and Relapser

<table>
<thead>
<tr>
<th>PR</th>
<th>PR+ BOC RGT</th>
<th>PR+ BOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>(15/51)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>(31/26)</td>
<td>(72/105)</td>
</tr>
<tr>
<td>75</td>
<td>(77/103)</td>
<td>92</td>
</tr>
</tbody>
</table>

PR = Partial Responder, BOC = Boceprevir, RGT = Ribavirin

SVR in Advanced Fibrosis/Cirrhosis

Recommendation: All cirrhotic patients receiving BOC + PR should receive 48 weeks of therapy[1,2]

Subgroup Analysis of SPRINT-2 and RESPOND-2

SVR by Week 4 PR Lead-In Response

Poorly Responsive to IFN: <1 log10 viral load decline at treatment week 4
Responsive to IFN: ≥1 log10 viral load decline at treatment week 4


 PROVIDE Study: SVR Rates by Prior Treatment Response

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>SVR (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nulls</td>
</tr>
<tr>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>67%</td>
<td>13%</td>
</tr>
<tr>
<td>93%</td>
<td>6%</td>
</tr>
</tbody>
</table>

All includes: Nulls, Partial, Relapsers and Others


Resistance-Associated Variants Develop When SVR Not Achieved

- Recommendation: Patients with virologic failure on one PI should not be retreated with the other.
- Similar mutations selected in resistance-associated variants detectable in patients failing BOC or TVR.
- Clinical significance of resistance-associated variants unknown.
- Predominant strain returns to wild type in majority within 2 yrs.
  - Slower process in subtype 1a
- Recommendation: Follow stopping rules strictly to minimize selection of resistance-associated variants.


TVR: Severe Rash

- Generalized rash, or rash with vesicles, bullae, or ulcerations
- No Stevens Johnson Syndrome/DRESS
- Stop telaprevir, if no improvement in 7 days, stop PR
- Do not reintroduce telaprevir
- If no improvement, refer to Dermatologist
Stevens-Johnson Syndrome (SJS) / Drug Rash With Eosinophilia and Systemic Symptoms (DRESS)

- SJS: Fever, target lesions, mucosal erosions/ulcerations
- Drug rash with eosinophilia and systemic symptoms
  - Rash, fever, facial edema, internal organ involvement
  - ± eosinophilia
- Stop all medicines
- Urgent dermatology referral

Gastrointestinal Side effects

- Nausea: promethazine, ondansetron
- TVR should be taken with 20 g of fat to help with absorption
- Perianal symptoms
  - Anal pruritus with TVR: antihistamines
  - Topical therapies: witch hazel topical, hydrocortisone cream, mesalamine suppositories,
  - Topical lidocaine for perineal pain
- Diarrhea: loperamide, bulk/fiber supplement

ADVANCE/ILLUMINATE: Anemia and RBV Dose Reduction Did Not Affect SVR in TVR Arms

Anemia: Hgb <10 g/dL

Anemia | No Anemia | RBV Dose Reduction | No RBV Dose Reduction
--------|----------|---------------------|---------------------
145/196 | 116/165  | 247/344             | 44/92               |
206/265 | 173/255  | 164/534             | 135/262             |
135/172 | 106/148  | 241/300             | 37/48               |
226/293 | 163/272  | 434/545             | 117/245             |
Anemia

- Mechanism of anemia thought to be result of bone marrow suppressive effect associated with agents, not due to RBC hemolysis. Compared to PR:
  - Patients treated with TVR had:
    - Higher frequency of anemia, Hgb level <10 g/dL (36% vs 17%)
    - Higher frequency of Hgb reductions to Grade 3+ toxicity (7.0 to <8.9 g/dL or any decrease >4.5 m/dL) levels (55% vs 25%)
    - Higher frequency of Hgb level <8.5 g/dL (14% vs 5%)
    - More anemia-related SAEs (2.5% vs <1%)
    - Higher frequency of anemia-related discontinuations (4% vs <1%)
  - Patients treated with BOC had:
    - Average additional decrease of Hgb of approximately 1 g/dL
    - Anemia reported as a SAE (1% vs none with PR)
    - A higher frequency of Hgb reductions to Grade 3+ toxicity

A Randomized Trial Comparing RBV Dose Reduction vs EPO for Anemia Management in Previously Untreated Patients With Chronic Hep C Receiving PR + BOC

- End-of-treatment response, relapse, and SVR were comparable between RBV DR and EPO arms

![Chart showing SVR by Secondary Anemia Intervention (cont)](chart)

Anemia: Management Recommendations With TVR- or BOC-based Therapy

• Monitoring: CBC pretreatment, every 2 weeks until treatment week 8, then monthly
• Week 1 CBC in those with advanced fibrosis
• Primary strategy: RBV dose reduction
  • BOC—Hgb <10 g/dL: decrease in dosage by 200 mg
  • TVR—When anemia occurs, first RBV reduction to 600 mg
  • Hgb <8.5 g/dL: PI says to stop all therapy
    • Consider secondary anemia strategies: EPO, further RBV dose reduction, transfusion
    • Transfusions occurred in phase 3 trials and occur in clinical practice
• If RBV is permanently D/C, BOC or TVR also must be D/C
• Do not reduce PI dose to manage anemia

Futility Rules for BOC or TVR + PR

• Recommendation: All therapy should be discontinued in patients with the following

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Criteria</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 12</td>
<td>HCV RNA ≥100 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>HCV RNA detectable</td>
<td>Discontinue all therapy</td>
</tr>
</tbody>
</table>

Recommendation: < 1 log reduction with lead-in, DC if less than 3 log reduction at week 8 with boceprevir

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Criteria</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4 or 12</td>
<td>HCV RNA &gt;1000 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>HCV RNA detectable</td>
<td>Discontinue TVR</td>
</tr>
</tbody>
</table>

Assay should have a lower limit of HCV RNA quantification of ≤25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.


Summary

• Both TVR and BOC added to PR improve SVR rates.
• Now at least half of individuals can be treated for 6 mos.
  • IL-28B CC predicts 6 month duration of treatment
  • On treatment response, lead-in eRVR also predict response
• TVR: Rash, GI side effects, anemia
• BOC: Anemia, dysgeusia
• Careful monitoring, especially in those with advanced fibrosis
• Identify consultants prior to initiating therapy.
  • Dermatologist
• Drug-drug interactions must be assessed.
  • virtually all interactions can be addressed
Direct-Acting Antiviral Agents (DAAs) - Key Characteristics

- **NS3/4A Inhibitors (Protease inhibitor PI)**
  - High potency
  - Limited genotypic coverage
  - Low barrier to resistance

- **NS5B Nucleos(t)ide Inhibitors (NI)**
  - Intermediate potency
  - Pan genotypic coverage
  - High barrier to resistance

- **NS5A Inhibitors**
  - High potency
  - Multi-genotypic coverage
  - Low barrier to resistance

- **NS5B Non Nucleoside Inhibitors (NNI)**
  - Intermediate potency
  - Limited genotypic coverage
  - Low barrier to resistance

What Is in Our Near Future? More Triple Therapy

- DAA plus IFN backbone plus ribavirin (RBV)
  - Second-generation PIs
  - Nucleoside polymerase inhibitors
  - Nonstructural protein (NS)5A inhibitors

- EXPECTATIONS
  - RVR >90%
  - Sustained virologic response (SVR): >80%
  - Tolerability and side effects
  - RGT

Two New Protease Inhibitors Are Coming in Combination With PEG IFN/RBV

- **Simeprevir**
  - NS3 protease inhibitor
  - Q daily dosing
  - Improved side effect profile
  - No anemia
  - Fewer DDIs

- **Faldaprevir**
  - NS Protease inhibitor
  - Q daily dosing
  - Improved side effect profile
  - No anemia
QUEST-1 and QUEST-2: Simeprevir (PI) + PegIFN + RBV in Treatment-Naive GT1

- 85%-91% qualified for shortened therapy
- Baseline Q80K mutation in genotype 1a may affect SVR

![Chart showing patients achieving SVR12 (%)](chart1.png)

STARTVerso: Primary Endpoint SVR12 (ITT)

- 87%-89% Qualified for Short Duration Therapy

![Chart showing SVR12 rates adjusted for race and genotype](chart2.png)

Sofosbuvir (SOF, GS-7977)

- HCV-specific nucleotide polymerase inhibitor (chain terminator)
- Potent antiviral activity against HCV genotypes 1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Favorable clinical pharmacology profile
  - No food effect
  - No significant drug interactions
- Generally safe and well tolerated in clinical studies to date (>2000 patients)
  - No safety signal in preclinical clinical studies

![Chemical structure of Sofosbuvir](structure.png)
**NEUTRINO Study: 12 Weeks of Sofosbuvir + PEG IFN/RBV**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients with HCV RNA &lt;LLOQ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>295/327 (91)</td>
</tr>
<tr>
<td>GT 1</td>
<td>261/293 (89)</td>
</tr>
<tr>
<td>GT 4</td>
<td>27/28 (96)</td>
</tr>
<tr>
<td>GT 5,6</td>
<td>7/7 (100)</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.


---

**Multiple All Oral Regimens in Clinical Trials**

- Nucleotide analogue polymerase inhibitor alone or plus NS5A inhibitor
  - Sofosbuvir + RBV
  - Sofosbuvir + daclatasvir ± RBV
  - Sofosbuvir + GS5685 + RBV
- Protease inhibitor + NS5A inhibitor ± non-nucleoside polymerase inhibitor ± RBV
  - ABT450/r + ABT267 + ABT333 ± RBV
  - Asunaprevir + daclatasvir ± BMS-325
  - Faldaprevir + BI7227 + RBV

---

**ELECTRON: Sofosbuvir + Ledipasvir 12 Week Regimens in GT1**

<table>
<thead>
<tr>
<th></th>
<th>SOF + LDV</th>
<th>SOF + LDV + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>naive (n=25)</td>
<td>null (n=10)</td>
</tr>
<tr>
<td>Week 1</td>
<td>8/25 (32)</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>Week 2</td>
<td>17/25 (68)</td>
<td>7/10 (70)</td>
</tr>
<tr>
<td>Week 4</td>
<td>25/25 (100)</td>
<td>10/10 (100)</td>
</tr>
<tr>
<td>EOT</td>
<td>25/25 (100)</td>
<td>10/10 (100)</td>
</tr>
<tr>
<td>SVR4</td>
<td>22/25 (88)</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>SVR12</td>
<td>21/25 (84)</td>
<td>1/10 (10)</td>
</tr>
</tbody>
</table>

* Analyzed by TaqMan® HCV Test 2.0 with limit of detection (LOD) of 15 IU/mL.
† Includes 1 patient who stopped all treatment due to a serious adverse event (AE) at Week 8, this patient subsequently achieved SVR12.

AVIATOR Study: ABT-450/r, ABT-267, ABT-333 ± RBV in Non-Cirrhotic, Naïve and Null Responders

<table>
<thead>
<tr>
<th>Regimen/Duration</th>
<th>SVR12</th>
<th>SVR24*</th>
<th>Breakthrough/Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>89</td>
<td>88</td>
<td>0/10</td>
</tr>
<tr>
<td>ABT-450 ABT-267 RBV</td>
<td>85</td>
<td>83</td>
<td>1/4</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333</td>
<td>91</td>
<td>89</td>
<td>1/8</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>90</td>
<td>87</td>
<td>1/5</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>99</td>
<td>96</td>
<td>0/1</td>
</tr>
<tr>
<td>ABT-450 ABT-267 RBV</td>
<td>93</td>
<td>90</td>
<td>0/2</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>89</td>
<td>89</td>
<td>0/5</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>93</td>
<td>93</td>
<td>3/0</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>98</td>
<td>95</td>
<td>1/0</td>
</tr>
</tbody>
</table>

N = 571

* 8 patients with SVR12 have not returned for >24 weeks and are counted as virologic failures for SVR24;
  3 patients relapsed between SVR12 and SVR24.


Faldaprevir (PI) + BI 207127
With or Without RBV

SOUND-C2 Study Sub-analysis:
Efficacy/Safety of the IFN-free Combination of BI 201335 + BI 207127 ± RBV in Treatment-naive G1 Patients With Compensated Liver Cirrhosis

- Safety and tolerability profile good – did not differ significantly in cirrhotics vs non-cirrhotics
- Plasma exposure of faldaprevir and BI 207127 higher in cirrhotics (less apparent in BID arm)

Evolution of Therapy in HCV G1

Genotypes 2/3 will have an oral regimen first

FISSION Study: Treatment-Naive, Genotype 2 or 3 Patients

<table>
<thead>
<tr>
<th>Week</th>
<th>SOF + RBV, n=256</th>
<th>Peg-IFN + RBV*, n=243</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>SVR12</td>
<td>SVR12</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SOF + RBV, n=256

- Mean age, y (range): 48 (20–72)
- Male, n (%): 171 (67)
- White, n (%): 223 (87)
- IL28B CC, n (%): 108 (43)
- GT 3, n (%): 183 (72)
- Mean HCV RNA, log_{10} IU/mL (range): 6.0 (3.2–8.3)
- Cirrhosis, n (%): 50 (20)

Peg-IFN + RBV*, n=243

- Mean age, y (range): 48 (19–77)
- Male, n (%): 156 (64)
- White, n (%): 212 (87)
- IL28B CC, n (%): 106 (44)
- GT 3, n (%): 176 (73)
- Mean HCV RNA, log_{10} IU/mL (range): 6.0 (3.2–7.6)
- Cirrhosis, n (%): 50 (21)

*RBV dose: 1,000–1,200 mg/day for SOF + RBV and 800 mg/day for Peg-IFN + RBV

Gane E, et al. EASL 2013. Abst. 5.
Results: Virologic Response

<table>
<thead>
<tr>
<th></th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 12</th>
<th>On-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>23/251</td>
<td>76/241</td>
<td>249/250</td>
<td>158/236</td>
<td>242/244</td>
</tr>
<tr>
<td>Week 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study met primary endpoint of non-inferiority of SOF + RBV to Peg-IFN + RBV. Error bars represent 95% confidence intervals.


Hepatitis C Therapy Will Parallel Helicobacter pylori Therapy

Conclusion

- **Testing and Assessment**
  - Diagnosing and classifying HCV
  - Assessment of likelihood of SVR

- **Treatment**
  - Guideline recommendations
  - Individualizing therapy
  - Utilizing newly approved agents
  - Managing comorbidities
  - Managing side effects
  - Emerging therapies
Click on the Question Bank tab to listen to responses to questions asked during live sessions.

TO RECEIVE CME CREDIT PLEASE COMPLETE THE POST-PROGRAM SURVEY AND EVALUATION.